Minutes of Meeting

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee

May 14, 2008

Attendees: Chairman Dr. Joseph Thomas, Ms. Sheri Lynn Boston, Dr. Gerard J. Ferris, Dr. Nan Ferris, Dr. Michelle S. Freeman, Dr. James Gagnon, Ms. Vicki Little Faulk, Dr. Kelli Littlejohn, Mr. Ben Main, Dr. Robert Moon, Dr. Nancy J. Sawyer, and Dr. Chivers R. Woodruff

Absent: Dr. Lucy Culpepper

1. **OPENING REMARKS**
   Vice-chairman Main called the Pharmacy and Therapeutics (P&T) Committee Meeting to order at 9:00 a.m.

2. **APPROVAL OF MINUTES**
   Vice-chairman Main asked if there were any corrections to the minutes from the February 20, 2008 P&T Committee Meeting. Since there were no corrections, a motion was made and seconded to approve the minutes.

3. **PHARMACY PROGRAM UPDATE**
   Dr. Littlejohn announced that on March 23, 2008, the agency implemented a new MMIS system called "Interchange" and recognized all individuals who have contributed to this implementation.

   On April 1, 2008, the Agency implemented the federal requirement that any outpatient non-electronic prescription be written on a Tamper Resistant Prescription Pad. More information concerning this can be found on the Agency's web site.

   On May 1, 2008, the Agency implemented a Dispense as Written (DAW) edit. All claims with a DAW code of 1 will require an override and a Food and Drug Administration (FDA) MedWatch Form 3500 with exceptions being made for phenytoin, carbamazepine, warfarin, and levothyroxine drug products. Dr. Littlejohn also noted that due to a recent Class I recall on generic digoxin an exception has also been made for the brand Lanoxin®. This exception will be lifted once the generic is again fully available.

   Dr. Littlejohn announced that the Pharmacy Program is working on four new projects. The Agency is currently working with pharmacy associations on a cost of dispensing study as well as the development of a new state Maximum Allowable Cost (MAC) program. In addition the Agency has posted an Invitation to Bid for their prior-authorization administrative and clinical contracts as both contracts with the current vendors will expire later this year.

   A Positive Antipsychotic Management (PAM) update was provided and it was noted that as requested by the P&T Committee the Agency has met with the Department of Mental Health, a group of child psychiatrists and other specialists to discuss antipsychotic utilization in Alabama. There have been two meetings with a third planned for this summer.

Dr. Littlejohn addressed the manufacturing/industry representatives with an issue that has come to the Agency's attention, noting that all P&T Committee members are expected to uphold the charge of the P&T Committee and before serving their term are required to sign a Statement of Integrity, which includes a statement "I agree not to have ex parte contacts or discussions with manufacturers or representatives whose drugs are presented for review". While it is understood there is a level of coordination between members of the manufacturing industry and providers through the normal course of business, she asked the manufacturers to respect the P&T charge and Statement of Integrity by not soliciting the P&T members regarding drugs to be reviewed in an upcoming P&T meeting. Chairman Thomas and Dr. Woodruff inquired if something in writing could be provided to the P&T members allowing them to have it readily available to share with industry representatives if needed. Dr. Littlejohn replied that this could be provided to the members. Chairman Thomas then noted that this may be something that could be put into the Physicians' Newsletter.

4. ORAL PRESENTATIONS BY MANUFACTURERS/MANUFACTURERS' REPRESENTATIVES

Five-minute verbal presentations were made on behalf of some pharmaceutical manufacturers. Dr. Littlejohn explained the process and timing system for the manufacturers' oral presentations. The drugs and corresponding manufacturers are listed below with the appropriate therapeutic class. There were a total of nine manufacturers' verbal presentations at the meeting.

5. PHARMACOTHERAPY CLASS REVIEWS (Please refer to the web site for full text reviews.)

The pharmacotherapy reviews began at approximately 9:10 a.m.

Platelet-aggregation Inhibitors American Hospital Formulary Service (AHFS) 201218

Manufacturer comments on behalf of these products:

Plavix® (clopidogrel)-Sanofi Aventis

Dr. N. Ferris began her presentation by noting that platelet-aggregation inhibitors, also known as antiplatelet agents, play a major role in the management of cardiovascular, cerebrovascular and peripheral vascular diseases. Since the previous review in February 2006, there have been no significant changes with regards to the addition of any new generic or brand products introduced to the market. Aspirin, cilostazol, dipyridamole and ticlopidine are all available generically and are currently on the Alabama Medicaid Preferred Drug List (PDL). Aggrenox® (the fixed-dose combination product containing aspirin and extended release [ER] dipyridamole) and Plavix® (clopidogrel) are not available generically and are not on the Alabama Medicaid PDL.

Current treatment guidelines that incorporate the use of the platelet-aggregation inhibitors were discussed. The American Heart Association (AHA) and American Stroke Association Council on Stroke (2006) recommend aspirin, the combination of aspirin and ER dipyridamole, and clopidogrel as acceptable options for initial therapy for patients with noncardioembolic ischemic stroke or transient ischemic attack (TIA). The combination of aspirin and ER dipyridamole "is suggested" instead of aspirin alone, and clopidogrel "may be considered" instead of aspirin alone. The American College of Cardiology (ACC) and AHA recommend aspirin indefinitely for patients who have experienced unstable angina or non–ST elevation myocardial infarction (acute coronary syndrome [ACS]) and are treated medically without stenting. Clopidogrel should be prescribed for at least 1 month and ideally for up to 1 year. For aspirin-allergic patients, use clopidogrel alone (indefinitely) or try aspirin desensitization. For clopidogrel-allergic patients, use ticlopidine. Dual antiplatelet therapy with aspirin and clopidogrel is also recommended for patients undergoing stent implantation. The consensus guidelines recommend aspirin for patients with chronic stable angina. The ACC/AHA recommends antiplatelet therapy to reduce the risk of myocardial

infarction, stroke or vascular death in individuals with atherosclerotic lower extremity peripheral arterial disease. Aspirin is considered safe and effective with clopidogrel recommended as an effective alternative antiplatelet therapy. Cilostazol is recommended for intermittent claudication. Dr. N. Ferris mentioned that the 2003 American Diabetes Association (ADA) Consensus Statement on Peripheral Arterial Disease in People with Diabetes recommend antiplatelet agents (eg, aspirin or clopidogrel) for patients with diabetes based on the CAPRIE study. The ADA states that patients with diabetes and peripheral arterial disease may benefit more by taking clopidogrel.

The Food and Drug Administration (FDA)-approved indications for the platelet-aggregation inhibitors were briefly discussed. Aspirin and clopidogrel are approved for secondary prevention of both cardiovascular and cerebrovascular events. Clopidogrel is also indicated to reduce the atherothrombotic events in patients with established peripheral arterial disease. The fixed-dose combination product containing aspirin and dipyridamole (Aggrenox®) is only indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or stroke.

Key pivotal clinical studies evaluating the safety and efficacy of the platelet-aggregation inhibitors were highlighted. The European Stroke Prevention Study 2 compared monotherapy with aspirin or dipyridamole to the fixed-dose combination product (Aggrenox®) in patients who had experienced an ischemic stroke or TIA. In comparison to placebo, stroke risk was reduced by 18% with aspirin alone, 37% with the fixed-dose combination product of aspirin and ER dipyridamole and 16% with dipyridamole alone. The ESPRIT Study Group reported that dipyridamole plus aspirin significantly reduced the composite of death, stroke, myocardial infarction, and major bleeding to 13% of patients compared to 16% for aspirin monotherapy; however, the combination regimen was discontinued more often, mainly because of headache.

The CAPRIE study reported that clopidogrel significantly reduced the combined risk of ischemic stroke, myocardial infarction and vascular death by 8.7% compared to aspirin in patients with a recent ischemic stroke, myocardial infarction or established peripheral vascular disease. The greatest benefit was observed in patients who were admitted to the study with established peripheral arterial disease. On the basis of the CURE, COMMIT and CLARITY studies, clopidogrel received FDA approval for patients with ACS and myocardial infarction.

The platelet-aggregation inhibitors play an important role in the treatment and prevention of cerebrovascular and cardiovascular diseases. Aspirin, cilostazol, dipyridamole and ticlopidine are available generically, and aspirin is available in several over-the-counter (OTC) formulations. Aggrenox® is not interchangeable with the commercially available generic formulations of aspirin and dipyridamole since the strengths and delivery mechanisms are different among these products.

Aspirin has been the most frequently studied platelet-aggregation inhibitor and is usually the reference drug to which other treatments are compared. Aspirin is the platelet-aggregation inhibitor recommended as first line in most treatment guidelines for general use. Other platelet-aggregation inhibitors are usually reserved for patients with contraindications or severe intolerance to aspirin or who have failed aspirin monotherapy, or in high-risk patients when dual antiplatelet therapy is recommended (eg, acute coronary syndrome, recent myocardial infarction, stent implantation).

For patients with noncardioembolic ischemic strokes or TIAs, the consensus guidelines state that the combination of aspirin and ER dipyridamole is suggested instead of aspirin alone, and clopidogrel may be considered instead of aspirin alone to reduce the risk of recurrent stroke and other cardiovascular events.

At this time, there are no published head-to-head clinical trials comparing the fixed-dose combination product of aspirin and ER dipyridamole to clopidogrel for secondary prevention of ischemic strokes. The results of the PROFESS trial are expected to be released in 2008. There are no studies that have compared the safety and efficacy of administration of the fixed-dose combination product to administration of the individual ingredients.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use. Clopidogrel (Plavix®) and the fixed-dose combination product containing aspirin and ER dipyridamole (Aggrenox®) should be available as first-line therapy for patients who have experienced an ischemic stroke or TIA through the medical justification portion of the prior-authorization (PA) process. Clopidogrel should be available as first-line therapy for patients with established peripheral arterial disease as an alternative to aspirin. Clopidogrel should also be available as first-line therapy in combination with aspirin for patients experiencing ACS and/or acute myocardial infarction and/or undergoing percutaneous coronary interventions through the medical justification portion of the PA process.

No brand platelet-aggregation inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Dr. Sawyer stated that she had received a letter from the Comprehensive Stroke Center at UAB that stated that the fixed-dose combination product of aspirin and ER dipyridamole was the mainstay of treatment for patients with a TIA. Dr. N. Ferris replied that currently there are no published head-to-head trials comparing the fixed-dose combination product of aspirin and ER dipyridamole to clopidogrel. Chairman Thomas inquired if this topic could be revisited if more information were to become available. Dr. Littlejohn replied that topics can come back to the P&T at the request of the Committee or the manufacturer per the policy posted on the website.

Mr. Main inquired when clopidogrel would be used first line. Dr. N. Ferris replied by listing the indications, reiterating the guidelines, and explaining the criteria. Ms. Boston then inquired what would be considered "general use". Dr. N. Ferris replied that it would consist of patients with no significant underlying condition(s) or a patient population without significant risk factors or event(s). Chairman Thomas then inquired how the dose of aspirin is determined and if serum levels could be taken. Dr. N. Ferris replied that the dose is based on the published studies, including meta-analysis, with the goal to optimize the lowest dose with the best benefit.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Antiarrhythmic Agents AHFS 240404
Manufacturer comments on behalf of these products:
None

Dr. Gagnon noted that since the last review 2 products have been discontinued by the manufacturer (moricizine and procainamide sustained-release tablets). It was noted that all of the antiarrhythmic agents, with the exception of dofetilide, moricizine, and sustained-release propafenone, are available generically.

Treatment guidelines incorporating the use of the antiarrhythmic agents were discussed. National and international treatment guidelines state that the antiarrhythmics are generally not recommended as first-line agents for the treatment of ventricular arrhythmias. Amiodarone and sotalol may be used to treat ventricular tachycardias in patients with left ventricular dysfunction due to a prior myocardial infarction and who are not responding to β-blockade from other agents. In those patients with atrial fibrillation, rate control is the recommended treatment strategy but rhythm control may be appropriate in certain circumstances, particularly in patients whose quality of life is affected by atrial fibrillation.

Dr. Gagnon discussed the safety of the antiarrhythmic agents. Although the drug interactions and adverse events vary from one agent in the class to another, all of the agents in the class are associated with a number of drug interactions and adverse events. In addition, the antiarrhythmic agents are associated with black box warnings. Due to adverse events, drug interactions, and black box warnings, many patients cannot tolerate these agents or simply cannot use them due to concurrent medical conditions.

Clinical trials measuring the safety and efficacy of the antiarrhythmic agents were discussed. The agents in this class have been shown to be effective when used in the appropriate patient populations for their FDA-approved indications. However, several clinical trials have demonstrated the safety concerns.

The antiarrhythmic agents exert their pharmacologic properties through a wide range of mechanisms and they are used to treat various atrial and ventricular arrhythmias. They also differ in their pharmacokinetic, drug interaction and side effect profiles. The FDA-approved indications differ between agents and may include atrial arrhythmias and/or ventricular arrhythmias. With the exceptions of dofetilide, moricizine and sustained-release propafenone, all other antiarrhythmics reviewed are available in generic formulations.

Adverse events and major drug interactions are common among the antiarrhythmic agents and these properties tend to limit their use in clinical practice. Several clinical trials have demonstrated these adverse events.

Guidelines incorporating the use of antiarrhythmic agents state that they are generally not recommended as first-line agents for the treatment of ventricular arrhythmias and that there are many factors that should be addressed prior to the selection of an antiarrhythmic agent for a patient, including the type of arrhythmia, concurrent disease states, and potential risk-to-benefit ratio of therapy.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand antiarrhythmic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Cardiotonic Agents AHFS 240408
Manufacturer comments on behalf of these products:
None

Dr. Gagnon noted that the cardiotonic agent, digoxin, is a cardiac glycoside and is extracted from the leaves of the *Digitalis lanata* plant. The efficacy of digoxin in patients with heart failure and atrial fibrillation (AF) has been well established and widely accepted. Digoxin is available generically in both oral and injectable formulations.

National and international guidelines state that for the treatment of AF, digoxin should be considered a secondary agent to a β-blocker or nondihydropyridine calcium-channel blocker. For the treatment of chronic heart failure, guidelines state that digoxin may be added to concurrent therapy with diuretics, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a β-blocker in those patients with persistent heart failure symptoms or in those patients who have not yet responded to initial therapy.

Dr. Gagnon noted that the pharmacokinetics vary between the different dosage forms of digoxin. The safety of digoxin was discussed, including significant drug interactions and adverse drug events. The adverse drug events reported with digoxin are dose dependant and are less common when digoxin is used at recommended doses to achieve a therapeutic effect.

Dr. Gagnon stated that studies have demonstrated that digoxin is efficacious when used in the management of AF and chronic heart failure as national and international treatment guidelines recommend. Digoxin is FDA approved for the treatment of AF and heart failure. Although there are minor differences with respect to pharmacokinetic parameters, all digoxin formulations are equally effective. Due to its potential for drug interactions and other toxicities, digoxin therapy should be monitored closely.

Currently, there are several guidelines that discuss the role of digoxin therapy for the treatment of AF and heart failure. According to the current treatment guidelines for AF, digoxin is recommended as a second- or third-line agent. Digoxin may be used in specific patient populations including those that are sedentary, those who have concurrent heart failure, or those who cannot tolerate or have failed single therapy with β-adrenergic blocking agents and calcium channel blockers. In the current guidelines for the treatment of heart failure, it is recommended that digoxin may be added to standard therapy in those patients who continue to have symptoms of heart failure. In those patients with concurrent symptomatic heart failure and AF, digoxin should be used as the first-line agent.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand cardiotonic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Dr. Woodruff inquired about mislabeled generic products. Dr. Littlejohn discussed the recent Class I recall of digoxin and the Agency's response. Dr. Woodruff then inquired if the FDA randomly checks to see if generic agents are consistently bioequivalent. Dr. Gagnon replied that he was not aware of this and it was usually expected that manufacturers abide by good manufacturing practices. He also noted that reporting problems using the FDA's MedWatch form is one way that these issues come to light. Dr. Sawyer then noted the recent heparin recall as another example.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Miscellaneous Cardiac Drugs AHFS 240492
Manufacturer comments on behalf of these products:
None

Dr. Gagnon noted that ranolazine was FDA approved in January of 2006 for the treatment of chronic angina in combination with amlodipine, β-adrenergic blocking agents, or nitrates, in patients who have not achieved an adequate response with other antianginal agents. Ranolazine was reviewed as a new drug review in November of 2006. The mechanism of action of ranolazine was then discussed.

Dr. Gagnon stated that most guidelines do not address the use of ranolazine, as it was approved after their publication dates or has not been approved in their host countries. The ACC/AHA guideline on Unstable Angina and Non–ST-segment Elevation Myocardial Infarction (UA/NSTEMI), states that when used in accordance with its FDA-approved indication, ranolazine may be safely administered for symptom relief after UA/NSTEMI but it does not appear to significantly improve underlying disease. The European Society of Cardiology does mention ranolazine in their Management of Stable Angina Pectoris guideline but no recommendations were issued concerning its use. The European Society of Cardiology notes in their Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-segment Elevation guideline that ranolazine exerts antianginal effects by inhibiting the late sodium current but it was not effective in reducing major cardiovascular events in the MERLIN-TIMI trial.

It was noted that ranolazine is almost completely metabolized by the cytochrome P450 isoenzyme system. Therefore, the potential for numerous drug interactions exists. It was also discussed that ranolazine has been shown to prolong the QT interval in a dose-dependent manner and that the relationship between ranolazine and QT interval is linear. However, the full clinical significance of this QT prolongation effect is not known.

Clinical studies evaluating the safety and efficacy of the miscellaneous cardiac drugs (ranolazine) were discussed. Ranolazine has been shown to significantly improve exercise duration and time to onset of angina as well as reduce angina frequency and nitroglycerin usage. Rousseau and colleagues demonstrated that the immediate-release formulation of ranolazine, when compared to atenolol, increased exercise duration. However, ranolazine proved similar to atenolol in its effect on other anginal symptoms such as time to angina, angina frequency, and nitroglycerin use. The MERLIN-TIMI trial was then discussed.

The only agent classified as a miscellaneous cardiac drug is ranolazine. It is an antianginal drug that has been shown to be efficacious and is FDA approved for use in combination with nitrates, β-adrenergic blocking agents, or amlodipine.

A significant concern with ranolazine is its potential for QT prolongation. Therefore, ranolazine should be avoided in patients with pre-existing QT prolongation, who are taking QT-prolonging drugs or potent or moderately potent CYP3A inhibitors or patients with any type of hepatic impairment or severe renal impairment. Due to the dose-dependent potential for QT prolongation, the manufacturer has recommended that ranolazine be reserved for patients that have shown inadequate response to other antianginal drugs. Most current guidelines do not address the use of ranolazine, as it was approved after their publication dates or has not been approved in their host countries. Currently there is limited data comparing

ranolazine to other currently available antianginal agents such as β-adrenergic blocking agents, calcium channel blockers, and long-acting nitrates.

Therefore, since ranolazine should be reserved for use in combination with other antianginal agents in those patients who have not achieved an adequate response with other antianginal drugs, it is advisable that this agent be managed through the existing medical justification portion of the PA process.

No brand miscellaneous cardiac drug is recommended for preferred status, regardless of cost.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Bile Acid Sequestrants AHFS 240604
Manufacturer comments on behalf of these products:
None

Dr. N. Ferris stated that the antilipemic agents were broken down by the AHFS into 5 different classes: the bile acid sequestrants, the cholesterol absorption inhibitors, the fibric acid derivatives, the HMG-CoA reductase inhibitors (or statins) and the miscellaneous antilipemic agents. All of these therapeutic classes were previously reviewed in February 2006. There are 3 agents within the bile acid sequestrant class: cholestyramine, colesevelam and colestipol. Since the previous review, generic formulations for Colestid® tablets and granules have become available. Cholestyramine is also available generically. There are currently no brand bile acid sequestrants on the Alabama Medicaid PDL.

As their name implies, the bile acid sequestrants work by binding bile acids in the intestine to form an insoluble complex that is excreted in the feces. The bile acid sequestrants are primarily indicated as either monotherapy or in combination with a statin to reduce elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in primary hypercholesterolemia. In addition to the treatment of hypercholesterolemia, cholestyramine is also indicated for the relief of pruritus associated with partial biliary obstruction. Colesevelam recently received approval to improve glycemic control in adults with type 2 diabetes mellitus.

In general, most treatment guidelines recommend statin therapy as first-line treatment for lowering LDL-C. The guidelines recommend the use of bile acid sequestrants as an alternative for patients who have a contraindication or intolerance to a statin, or as additional treatment for patients who can not achieve goal cholesterol levels with monotherapy. The treatment guidelines do not give preference to one bile acid sequestrant over another.

The bile acid sequestrants are not absorbed. They have the potential to bind to other drugs, which may delay or reduce the absorption of concomitant oral medications. To minimize this interaction, other drugs should be taken at least 1 hour before or 4-6 hours after the bile acid sequestrants. The adverse effect profiles of the bile acid sequestrants are similar; gastrointestinal side effects are the primary complaint for all agents and these symptoms may diminish over time or may be relieved by increasing dietary fiber. All of the bile acid sequestrants can cause an increase in triglyceride levels, and therefore should not be utilized in patients with significantly elevated triglyceride levels.

Overall, these agents demonstrated moderate lipid-lowering capacity when compared to placebo, either alone or in combination with a statin. There are no head-to-head trials comparing the safety and efficacy

of one bile acid sequestrant to another. The Lipid Research Clinics Coronary Primary Prevention Trial compared cholestyramine to placebo in 3,800 asymptomatic males with primary hypercholesterolemia. Over approximately 7 years, cholestryamine reduced the risk of coronary heart disease or nonfatal myocardial infarction by 19% compared to placebo.

The bile acid sequestrant class includes cholestyramine, colesevelam and colestipol. Cholestyramine and colestipol are available generically. Treatment guidelines recommend statin therapy as first-line treatment for dyslipidemia. The guidelines recommend the use of bile acid sequestrants as an alternative for patients who have a contraindication or intolerance to a statin, or as additional treatment for patients who can not achieve goal cholesterol levels with monotherapy alone. All the bile acid sequestrants can be used in conjunction with a statin, or as monotherapy. Clinical trials demonstrate efficacy of each agent in reducing low-density lipoprotein, non–high-density lipoprotein, TC and other markers of dyslipidemia.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand bile acid sequestrant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Chairman Thomas inquired if there was a cholestyramine product available without a sweetener. Dr. N. Ferris replied that she was not aware of an available product.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Cholesterol Absorption Inhibitors AHFS 240605
Manufacturer comments on behalf of these products:
Zetia® (ezetimibe)-Merck/Schering-Plough

Like the previous class review of the cholesterol absorption inhibitors in February 2006, Dr. N. Ferris stated that ezetimibe is the only agent in this class and it is not currently on the Alabama Medicaid PDL. There are no generic or OTC products in this class. Ezetimibe reduces blood cholesterol by inhibiting the absorption of both dietary and biliary cholesterol by the small intestine. Most treatment guidelines recommend statin therapy as first-line treatment for dyslipidemia. The guidelines recommend the use of ezetimibe as an alternative for patients who have a contraindication or intolerance to a statin, or as additional treatment for patients who can not achieve goal cholesterol levels with monotherapy alone. Ezetimibe is primarily FDA approved for the treatment of hypercholesterolemia, either alone or in combination with a statin or fenofibrate.

The most common side effects of ezetimibe are gastrointestinal. Very rarely, ezetimibe has been associated with more serious side effects, such as hepatitis, myopathy and rhabdomyolysis.

In placebo-controlled trials, ezetimibe produced a 17%-18% decrease in LDL-C, which is comparable to the bile acid sequestrants. When added to a statin, ezetimibe produced additional reductions in LDL-C and more patients achieved their recommended target LDL-C goals with the combination regimen. While the clinical studies have shown ezetimibe is effective in lowering LDL-C, thus far, ezetimibe has not been

shown to alter cardiovascular outcomes. The recently published ENHANCE trial evaluated the efficacy of ezetimibe plus simvastatin compared to simvastatin alone in 720 patients with heterozygous familial hypercholesterolemia. The primary end point was the mean change in the intima-media thickness. No significant difference was found in this primary end point between simvastatin and ezetimibe compared to simvastatin alone during the two-year study period. Combination therapy with ezetimibe and simvastatin significantly lowered LDL-C by an additional 16.5% compared to simvastatin alone. Additional studies are necessary to determine if ezetimibe either alone or in combination with other lipid-lowering agents results in better clinical outcomes.

At this time, ezetimibe is the only cholesterol absorption inhibitor and appears to be a safe and modestly effective agent for the reduction of LDL-C. Additional data is necessary to determine its effects on high-density lipoprotein cholesterol (HDL-C) and triglycerides.

Statins are considered first-line agents for treating hyperlipidemia due to their ability to lower TC and LDL-C. As monotherapy, ezetimibe provides only modest reductions in LDL-C. Ezetimibe's primary role is in combination with a statin in patients unable to achieve or sustain target low-density lipoprotein levels on a statin alone or to reduce the dose of a statin required to achieve target levels.

Although studies have shown that the combination of ezetimibe and a statin is more efficacious in lowering LDL-C than monotherapy with either agent, the recently published results of the ENHANCE trial did not show that these reductions led to an improvement in a surrogate marker (intima-media thickness).

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand cholesterol absorption inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Dr. Moon inquired if there are any studies currently under way involving ezetimibe either alone or in combination with another statin looking at patient-oriented outcomes. Dr. N. Ferris replied that there could be but that she was not aware of any specific trials at this time. Dr. G. Ferris stated that theoretically any lipid lowering would benefit patient-oriented outcomes even if a study did not support it. Dr. N. Ferris agreed that theoretically this could be true. Dr. Sawyer inquired if a PA could be approved for the use of ezetimibe for fibromyalgia. Dr. N. Ferris replied that this would be handled through the medical justification portion of the PA process.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Fibric Acid Derivatives AHFS 240606
Manufacturer comments on behalf of these products:
None

Dr. N. Ferris began her presentation by stating that the therapeutic class called the fibric acid derivatives encompasses two chemical entities, fenofibrate and gemfibrozil. The fibric acid derivatives are established

as effective agents for managing dyslipidemia, particularly in patients with elevated concentrations of triglyceride-rich lipoproteins and low levels of HDL-C. Fenofibrate is available in several formulations including the micronized capsules and tablets and the nanocrystallized tablets. Since the previous review in February 2006, a new brand product (Lipofen®) and several generic formulations for micronized fenofibrate have been introduced to the market. Gemfibrozil (tablets) and micronized fenofibrate (capsules and tablets) are available generically.

While the statins are regarded as the cornerstone of lipid-modifying therapy, based on their proven efficacy in reducing plasma levels of LDL-C, they exert only modest effects on triglycerides and HDL-C. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) states that fibrates may have an adjunctive role in the treatment of patients with high triglycerides and low HDL-C, especially in combination with statins. Also, in high-risk patients with high triglyceride or low HDL levels, consideration can be given to combination therapy with fibrates or nicotinic acid and an LDL-C lowering agent. The consensus guidelines do not give preference to one fibric acid derivative over another.

There are some differences in the bioavailability of these fenofibrate products with regards to administration with food. The drug interaction between the fenofibrate and gemfibrozil and the statins is classified as a "Significance Level 1", which is considered of major severity. In general, the fibric acid derivatives are fairly well tolerated and there are no clear differences in regards to side effects.

Through the FIELD study, fenofibrate was shown to reduce patient-oriented outcomes of cardiovascular morbidity and mortality. Through the Helsinki Heart Group and VA-HIT, gemfibrozil was shown to reduce cardiovascular morbidity and mortality. There is only 1 published prospective trial that directly compared fenofibrate to gemfibrozil. Over a 6-week period, both agents produced comparable reductions in triglyceride levels. Reductions in LDL-C and TC were greater with fenofibrate compared to gemfibrozil. This trial was limited by the small sample size (N=21) and the fact that fenofibrate was not compared to gemfibrozil when administered at the recommended dose (which is 600 mg twice daily).

The fibric acid derivatives are used less frequently than statins, primarily because of a reduced LDL-C lowering capacity compared to statins; however, they have a greater capacity to reduce triglycerides compared to statins. The main place in therapy for fibric acid derivatives is for the treatment of hypertriglyceridemia in patients at risk for pancreatitis, and hypertriglyceridemia in patients with low HDL-C, especially with underlying diabetes, insulin resistance or the metabolic syndrome.

Gemfibrozil and fenofibrate are available generically. There are numerous formulations of fenofibrate, among which no particular product offers a distinct clinical advantage over another. There are no major clinically relevant differences between gemfibrozil and fenofibrate with regard to triglyceride-lowering efficacy, tolerability or safety. Notably, both gemfibrozil and fenofibrate are supported by clinical trials that show reductions in patient-oriented outcomes (coronary heart disease morbidity and/or mortality). However, neither product has demonstrated a decrease in all-cause mortality as has been shown with the statins. The national and international consensus treatment guidelines do not give preference to one fibric acid derivative over another. Both gemfibrozil and fenofibrate should be administered cautiously with a concomitant statin; however, there is evidence to suggest that fenofibrate may have less of an effect on statin metabolism and/or levels.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand fibric acid derivative is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

HMG-CoA Reductase Inhibitors Single Entity Agents AHFS 240608
Manufacturer comments on behalf of these products:
Crestor® (rosuvastatin)-AstraZeneca
Lipitor® (atorvastatin)-Pfizer

Dr. N. Ferris stated that since the previous review in February 2006, pravastatin and simvastatin have become available generically. Lovastatin is also available generically. While the statins exert a dose-dependent cholesterol-lowering capacity, in general, atorvastatin, rosuvastatin and simvastatin are considered the most potent statins.

For most patients, statins are recommended as first-line therapy due to their effectiveness in lowering LDL-C and the incidence of major coronary events and death in patients at risk for coronary or other atherosclerotic vascular diseases. The guidelines do not give preference to one statin over another. All of the statins are FDA approved for the management of hypercholesterolemia. Some of the statins are indicated for primary and/or secondary prevention of cardiovascular and/or cerebrovascular diseases. The safety and efficacy of rosuvastatin has not yet been established in children.

There are some differences in the pharmacokinetic parameters amongst the statins, which may result in differences in drug interactions. Statins are generally well tolerated. More serious but rare side effects of statins include increases in liver enzymes and myopathy, which can progress to rhabdomyolysis and acute renal failure. Consequently, liver function tests should be performed routinely with statin therapy.

Two main factors are typically considered when assessing the efficacy of statins: 1) the capacity to reduce LDL-C; and 2) outcomes data, specifically morbidity parameters (including primary and secondary prevention) and mortality. All of the statins have been shown to be effective in lowering LDL-C with atorvastatin, rosuvastatin and simvastatin demonstrating the highest potency. Atorvastatin, lovastatin, pravastatin and simvastatin have been shown to be effective in the primary and secondary prevention of cardiovascular disease. Positive patient outcomes have also been observed with statins, including those that are available generically. For example, the Heart Protection Study Group noted that simvastatin treatment over 5 years was associated with a 27% reduction in the incidence of first nonfatal or fatal myocardial infarction and 25% reduction in the incidence of first nonfatal or fatal stroke. The Scandinavian Simvastatin Survival Study Group noted that simvastatin therapy was associated with a 30% reduction in all-cause mortality compared with placebo.

The statins are primarily FDA approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia. Some of the statins are also indicated for primary and/or secondary prevention of cardiovascular events. Lovastatin, pravastatin, and simvastatin are available generically.

The agents in this class have demonstrated a significant benefit in reducing TC, LDL-C and triglycerides, and modestly increasing HDL-C. With the exception of rosuvastatin, the statins have been shown to reduce the risk of all-cause mortality, cardiovascular mortality, and cardiovascular morbidity. All of the statins have demonstrated the ability to delay the progression of coronary atherosclerosis among patients with and without established coronary heart disease. Furthermore, numerous studies have demonstrated the added benefit of aggressive lipid-lowering with statin therapy in reaching NCEP ATP III LDL-C goals as well as prolonging coronary heart disease-free survival.

While the statins differ in their LDL-lowering potential, there are no clinical studies that have demonstrated that one statin is more efficacious than another with regards to clinical outcomes. If LDL-C goal is not reached after 6 weeks of therapy with a statin, either an elevation of dose or the addition of a second lipid-lowering agent is appropriate.

At least one HMG-CoA reductase inhibitor (atorvastatin, lovastatin, pravastatin or simvastatin) that has demonstrated positive morbidity and mortality outcomes and at least one high-potency HMG-CoA reductase inhibitor (atorvastatin, rosuvastatin or simvastatin) should be available on the Alabama Medicaid PDL. Lovastatin, pravastatin and simvastatin are available generically and simvastatin fills both criteria. Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand single entity HMG-CoA reductase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Dr. Woodruff inquired if more potent was the same as more effective. Dr. N. Ferris replied that a statin with a higher potency reduces lipids to a greater extent. Chairman Thomas then inquired if it is possible to take enough of a lesser potent agent to equal a higher potent one. Dr. N. Ferris replied that is not always the case. Dr. Sawyer inquired if measuring for enzyme levels was indicative of myopathy. Dr. N. Ferris replied that it is just a marker and not always predictive of myopathy. Chairman Thomas inquired about the relative cost of some of the generic agents in the class when compared to some of the brands. Dr. N. Ferris replied that how long a generic has been available can impact the cost and over time more competition will become available resulting in a lower cost.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

HMG-CoA Reductase Inhibitors Combination Products AHFS 240608
Manufacturer comments on behalf of these products:
Caduet® (atorvastatin and amlodipine)-Pfizer
Vytorin® (simvastatin and ezetimibe)-Merck/Schering-Plough

Dr. N. Ferris stated that the combination statins include fixed-dose combinations of atorvastatin with amlodipine, lovastatin with ER niacin, and simvastatin with ezetimibe. There are no new agents in this class since the previous review. None of the combination products are available generically. Caduet® is currently on the Alabama Medicaid PDL.

The current treatment guidelines primarily focus on the management of dyslipidemias. Most consensus guidelines designate statins as first-line pharmacologic treatment of hypercholesterolemia. If LDL-C goal is not reached after 6 weeks of statin therapy, either an elevation of dose or the addition of a second agent, such as ezetimibe, niacin or a bile acid sequestrant, is recommended. Niacin may be preferred among patients with high triglycerides or low HDL-C levels. The guidelines do not directly address the role of statin fixed-dose combination products.

All of the combination statins are indicated for the management of hypercholesterolemia. They differ in their approval for primary and/or secondary prevention of cardiovascular or cerebrovascular events. The atorvastatin-amlodipine and lovastatin-niacin combination products are also indicated in patients for whom treatment with both components of the combination product is appropriate. In general, the pharmacokinetic, drug-interaction, and side-effect parameters with the combination statins are similar to their separate constituents.

Key pivotal clinical trials were discussed. Patients on the combination therapy, either as separate entities or the fixed-dose combination product, with atorvastatin and amlodipine experienced greater reductions in LDL-C and blood pressure than patients receiving monotherapy with either component. In addition, more patients reached their blood pressure and cholesterol target goals with combination therapy.

In the remaining trials comparing the addition of niacin or ezetimibe to a statin, combination therapy resulted in greater lowering of LDL-C. In addition, the niacin component significantly increased HDL-C and reduced triglycerides compared to monotherapy with either component. Although studies have shown that the combination of ezetimibe and a statin is more efficacious in improving lipid parameters than monotherapy with either agent, the recently published results of the ENHANCE trial did not show that these reductions led to better clinical outcomes. Additional studies are necessary to determine if the combination of ezetimibe plus a statin results in better clinical outcomes since no trial has yet demonstrated a reduction of cardiovascular outcomes with either ezetimibe alone or in combination therapy with a statin. A study by LaFleur did not report better adherence and persistence with the fixed-dose lovastatin and ER niacin product compared to administration of the separate components.

The combination HMG-CoA reductase inhibitors (statins) are FDA-approved for the treatment of primary hypercholesterolemia. Atorvastatin-amlodipine and lovastatin-niacin combination products are also indicated for the prevention of cardiovascular events. None of the combination products in this class are available generically but lovastatin, simvastatin and amlodipine are available generically.

The combination statins have demonstrated a significant benefit in reducing TC, LDL-C, triglycerides, and increasing HDL-C. Statins are used as first-line agents for the treatment of hypercholesterolemia and prevention of cardiovascular events. Niacin may increase HDL-C and lower triglycerides to a greater degree compared to statin monotherapy. When used in combination with statin therapy, patients evaluated in clinical studies were able to achieve greater LDL-C reduction compared to either niacin or statin monotherapy. Ezetimibe may be used as adjunctive therapy to statins in helping patients reach their NCEP ATP III targets for lipid levels. There are no studies that have demonstrated better clinical outcomes with the fixed-dose combination products compared to administration of the separate components.

Therefore, all brand products within the class reviewed are comparable to each other with regards to lipid parameters and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use. In general, HMG-CoA reductase inhibitor combination products do not offer any significant clinical advantage over administration of their individual components.

No brand combination HMG-CoA reductase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Dr. Woodruff asked why Caduet® was being reviewed as part of this class as one of its components lowers blood pressure. Dr. Littlejohn replied that the Agency was mandated through the PDL legislation to utilize the American Hospital Formulary Services (AHFS) drug classification system, and this is the AHFS class to which it has been assigned. Dr. Sawyer asked why Caduet® was currently on the PDL. Dr. N. Ferris replied that the recommendation the last time the class was reviewed was that no brand be preferred but to accept cost proposals. Dr. Littlejohn added that Caduet® was on the PDL due to the financial portion/supplemental rebate portion of the process. Dr. Woodruff inquired if patients had to use a combination product containing an agent to treat hypertension and an agent to treat dyslipidemia prior to having access to a combination product consisting of two lipid-lowering agents. Dr. N. Ferris replied no, that they could obtain a combination product consisting of two lipid-lowering agents either through medical justification or if they had tried and failed monotherapy with two or more preferred agents.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Miscellaneous Antilipemic Agents AHFS 240692
Manufacturer comments on behalf of these products:
None

Dr. N. Ferris began her presentation by stating that niacin and omega-3 acid ethyl esters are the only two agents classified as miscellaneous antilipemic agents by the AHFS. When this therapeutic class was previously reviewed in February 2006, the omega-3 acid ethyl esters were not included since they had not been on the market for at least 6 months. Both niacin and omega-3 acid ethyl esters are available as OTC and brand name prescription formulations. OTC niacin and prescription only Niacor® and Niaspan® are currently on the Alabama Medicaid PDL. Neither the OTC or prescription omega-3 acid ethyl esters are on the Alabama Medicaid PDL.

Prescription niacin and omega-3 acid ethyl esters are approved by the FDA as adjunctive agents for the treatment of hypertriglyceridemia. Prescription niacin has several other FDA indications, which include the management of hypercholesterolemia and mixed dyslipidemias. The NCEP ATP III states that in high-risk patients with high triglycerides or low HDL, consideration can be given to combination therapy with fibrates or nicotinic acid and an LDL-C lowering agent. The use of omega-3 acid ethyl esters was not addressed in this guideline. The AHA/ACC (2006) encourages increased consumption of omega-3 fatty acids in the form of fish or in capsule form for risk reduction in all patients with coronary and other atherosclerotic vascular disease. For lipid management, therapeutic options to reduce non-HDL-C include more intense LDL-C lowering therapy, or niacin or fibrate therapy. If triglycerides are $\geq$500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy. Dietary supplement niacin must not be used as a substitute for prescription niacin.

The most common adverse effects with niacin are gastrointestinal upset, flushing and pruritus. Flushing is more common with the immediate-release products. The frequency and severity of adverse hepatic effects appear to be dose related and may be increased with the sustained-release preparations. Sustained-release preparations have been hepatotoxic in doses $\geq$2 g per day. Cases of severe hepatotoxicity have occurred in

patients who have substituted sustained-release niacin for equivalent doses of immediate-release niacin. Therefore, different formulations should not be used interchangeably. Pooled data from randomized, placebo-controlled trials have shown that prescription omega-3 acid ethyl esters (Lovaza®) are safe and well tolerated. Omega-3 acid ethyl esters should be used with caution in patients with known hypersensitivity to fish or shell fish.

Key pivotal trials were discussed. The CDP Research Group reported that niacin treatment for 5 years significantly reduced the incidence of nonfatal myocardial infarction by 27% compared to placebo. In a follow-up of subjects 9 years after completion of the CDP study (which is the second study in the table), niacin significantly reduced the risk of all-cause mortality by 11%. The HATS and ARBITER 2 trials noted that niacin slowed progression or promoted regression of atherosclerotic disease in combination with other antilipemic agents in patients with a history of coronary artery disease and hypercholesterolemia.

The GISSI-Prevenzione Investigators reported that treatment with omega-3 polyunsaturated fatty acids significantly lowered the risk of the composite of death, nonfatal myocardial infarction and nonfatal stroke compared to no treatment. Prescription omega-3 acid ethyl esters were effective in lowering triglycerides and comparable to gemfibrozil.

Niacin and omega-3 acid ethyl esters are the only two agents classified by the AHFS as miscellaneous antilipemic agents. Niacin is available OTC and by prescription only in immediate-release and sustained-release formulations, which are currently on the Alabama Medicaid PDL. Omega-3 acid ethyl esters are also available OTC and by prescription only; however, the OTC products are not covered by Alabama Medicaid. There are no generic formulations for either legend niacin or omega-3 acid ethyl esters.

With regards to managing hypertriglyceridemia, clinical trials have shown that both niacin and omega-3 acid ethyl esters are effective in reducing triglyceride levels. There are no trials comparing the safety and efficacy of niacin to omega-3 acid ethyl esters. Prescription niacin has obtained additional indications since it has been shown to have favorable effects on all plasma lipoproteins and lipids.

While statins are considered the drugs of choice for lowering LDL-C, niacin is primarily used for the management of mixed hyperlipidemia, or as a second-line agent in combination therapy for hypercholesterolemia. There are limited head-to-head studies comparing the safety and efficacy of immediate-release to sustained-release niacin, but overall, these agents appear to be comparable in efficacy. While flushing may be more common with the immediate-release formulation, it still occurs with the sustained-release products. Different niacin formulations should not be used interchangeably and OTC niacin products must not be used as a substitute for prescription niacin.

Therefore, the prescription immediate-release and sustained-release niacin products are comparable to each other but do offer significant clinical advantages over other brand and OTC products within the class reviewed. Given its limited FDA-approved indication and potential for off-label use, prescription omega-3 acid ethyl esters should be available for patients with very high (≥500 mg/dL) triglyceride levels through the medical justification portion of the PA process.

Prescription niacin is recommended for preferred status. Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand prescription niacin product is selected as a preferred agent. No brand omega-3 acid ethyl ester is recommended for preferred status. Alabama

Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands**.**

Dr. G. Ferris inquired what the difference was between the immediate-release and sustained-release niacin products and if antihistamines could be used to reduce flushing. Dr. N. Ferris replied that there are limited head-to-head trials and that the current information shows more hepatotoxicity with the sustained-release and more flushing with the immediate-release products. She was aware that aspirin and ibuprofen were used to prevent flushing but was not aware of using antihistamines. Dr. G. Ferris then inquired why the nonprescription niacin was preferred, and if the all of the OTC products prepared by the various manufacturers were covered. Dr. Littlejohn replied that since it is an OTC agent it is automatically preferred and that the Agency can look into it if all of the different products were covered. Dr. Sawyer inquired if OTC niacin would remain on the PDL based on the proposed recommendations. Dr. N. Ferris replied that the proposed recommendations would not change the status of OTC niacin and that it would remain on the PDL.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Nitrates and Nitrites AHFS 241208
Manufacturer comments on behalf of these products:
None

Dr. Gagnon stated that the nitrates and nitrites are a class of vasodilating agents primarily indicated for the acute treatment, prophylaxis and management of angina pectoris due to coronary artery disease. Various formulations are available that differ in both onset and duration of action, which dictates their role in treatment of acute, stable and unstable angina. The development of tolerance limits the efficacy of all chronic nitrate therapies regardless of route of administration; however, nitrate-free interval dosing can limit the degree of tolerance associated with chronic use.

National and international guidelines state that short-acting nitroglycerin may be used for prompt relief or prevention of angina, and should be offered to all patients with stable angina. Guidelines also note that in the management of stable angina pectoris long-acting nitrates or calcium-channel blockers may be considered if β-adrenergic blocking agents are contraindicated or inadequately controlling symptoms. It is also noted that a nitrate-free regimen should be implemented to avoid tolerance.

Dr. Gagnon pointed out that the pharmacokinetics varies between the different dosage forms of the nitrates and nitrites. This difference reinforces that product selection is based on desired onset and duration of action.

Clinical trials evaluating the safety and efficacy of the nitrates and nitrites were discussed. Studies have found that isosorbide mononitrate results in a statistically significant improvement in exercise duration over placebo in patients with stable angina and that isosorbide dinitrate in combination with hydralazine has resulted in a 34% reduction in mortality in patients with heart failure compared to placebo ($P<0.028$).

The nitrates and nitrites are indicated for the acute, prophylactic and chronic treatment of angina pectoris due to coronary artery disease. Since all nitrates have the same pharmacologic effects, product selection is based on desired onset and duration of action. Nitroglycerin sublingual tablets have long demonstrated their utility as a treatment for acute angina due to their rapid onset of action. The nitroglycerin sublingual

spray possesses no known clinical advantage over the sublingual tablets. Isosorbide mononitrate and isosorbide dinitrate are available generically. Nitroglycerin extended-release capsules, injection, ointment, sublingual tablets, and transdermal patches are all available generically.

The potential for tolerance, and therefore loss of pharmacologic effect, is common to all nitrate formulations. Nitrate tolerance is minimized by ensuring a nitrate-free period and/or use of the lowest effective dose. The beneficial effects of nitrates for the management of chronic stable angina are evident although there is no known advantage over β-adrenergic blocking agents or calcium-channel blockers. Tolerance further limits the chronic use of this class of medications and as a result, they are considered second-line to β-adrenergic blocking agents for chronic stable angina.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand nitrate or nitrite is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

6. NEW DRUG REVIEWS

Veramyst® (fluticasone furoate) AHFS 520808 Intranasal Corticosteroids

Manufacturer comments on behalf of these products:

Veramyst® (fluticasone furoate)-GlaxoSmithKline

Dr. Gagnon noted that fluticasone furoate is a new nasally inhaled corticosteroid indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and children ≥2 years of age. Fluticasone furoate has demonstrated a binding affinity for the glucocorticoid receptor that is 1.7 times that of fluticasone propionate; however, the clinical relevance of this is unknown.

Treatment guidelines incorporating the use of the intranasal corticosteroids were discussed. Intranasal corticosteroids are considered the most effective treatment of allergic rhinitis and first-line therapy, particularly for moderate-to-severe allergic rhinitis. Guidelines do not designate one intranasal corticosteroid more effective than another.

Dr. Gagnon stated that the manufacturer advises that systemic and local corticosteroid use may result in the following: epistaxis, ulcerations, *Candida albicans* infection, impaired wound healing, cataracts, glaucoma, immunosuppression, and hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction.

Clinical trials evaluating the safety and efficacy of fluticasone furoate were discussed. Multiple studies have assessed the efficacy of fluticasone furoate compared to placebo in adult and adolescent patients with seasonal and perennial allergic rhinitis and in all studies fluticasone furoate was found to be generally well tolerated with headache and nosebleeds being the most common adverse events reported.

Three randomized controlled trials by Fokkens et al, Kaiser et al, and Martin et al, each 2 weeks in duration, were discussed. These studies found a significant improvement in nasal and/or ocular symptoms when compared to placebo. These studies also demonstrated a statistically significant improvement in quality of life scores for the active treatment ($P<0.001$). The safety and efficacy of fluticasone furoate in children 2-11 years of age was also discussed with one study demonstrating that the medication was more effective than placebo at both doses, but the difference was not always statistically significant. Although fluticasone furoate has not shown any adverse effects on growth in the pediatric population after 12 weeks of treatment, the effects of a longer duration of use has not been studied. Overall, there were no meaningful differences in safety end points with fluticasone furoate treatment in children when compared to placebo.

Fluticasone furoate is indicated for the treatment of symptoms associated with seasonal and perennial allergic rhinitis in adults and children ≥2 years of age. Despite a greater binding affinity for the glucocorticoid receptor, it is unclear whether fluticasone furoate offers any additional therapeutic benefit in comparison to fluticasone propionate or any other intranasal corticosteroid.

Multiple studies have assessed the efficacy of fluticasone furoate compared to placebo in patients with seasonal and perennial allergic rhinitis and found the agent to be safe and efficacious. There are no head-to-head trials comparing the efficacy and safety of fluticasone furoate nasal spray to other nasal corticosteroids for the management of perennial or seasonal allergic rhinitis.

The safety and efficacy of fluticasone furoate was evaluated in children 2-11 years old with seasonal or perennial allergic rhinitis in two studies for up to 12 weeks of treatment and although the medication did demonstrate efficacy over placebo, the difference did not always achieve statistical significance.

At this time, there is insufficient data to conclude that fluticasone furoate is safer or more efficacious than other brand or generic products within the class reviewed, and that it offers a significant clinical advantage over other alternatives in general use.

No brand fluticasone furoate is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Dr. G. Ferris inquired if any head-to-head trials with other intranasal corticosteroids had been published. Dr. Gagnon replied that no head-to-head trails had been published in peer-reviewed literature to date. There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Symbicort® (budesonide and formoterol fumarate) AHFS 680400 Orally Inhaled Corticosteroids
Manufacturer comments on behalf of these products:
Symbicort® (budesonide and formoterol fumarate)-AstraZeneca

Dr. Gagnon noted that budesonide and formoterol is a new combination product consisting of both an inhaled corticosteroid and a long-acting β_2-agonist. Budesonide, the inhaled corticosteroid, helps mediate the underlying airway inflammation associated with asthma while formoterol, the long-acting β_2-agonist, exerts its effects locally in the lungs to provide bronchodilation. This combination product is FDA approved for the long-term maintenance treatment of asthma in patients 12 years of age and older.

Dr. Gagnon stated that the pharmacological therapy for asthma is selected based upon the severity of the patient's disease. Clinical guidelines, including those from the National Heart, Lung, and Blood Institute, state that all patients should be prescribed a rescue inhaler such as albuterol, and that inhaled corticosteroids should be considered as the cornerstone of long-term control therapy. Patients whose asthma cannot be adequately controlled through monotherapy with an inhaled corticosteroid will normally require a step-up in therapy. Other national and international guidelines support the use of an inhaled corticosteroid with a long-acting β_2-agonist as treatment for patients with moderate-persistent to severe-persistent asthma that is inadequately controlled with inhaled corticosteroid monotherapy.

Dr. Gagnon noted that budesonide and formoterol should not be used to treat acute asthma symptoms or be initiated in patients during a rapidly deteriorating or potentially life-threatening asthma episode. A black box warning has been issued for the combination of budesonide and formoterol concerning the relationship between long-acting β_2-adrenerigc agonists and an increase in asthma-related deaths.

Clinical studies evaluating the safety and efficacy of the budesonide and formoterol combination products were discussed. Numerous studies have demonstrated the efficacy of the combination of budesonide and formoterol in the treatment of asthma when compared to placebo and to monotherapy. Head-to-head studies have compared the combination of budesonide and formoterol to fluticasone and salmeterol, another inhaled corticosteroid and long-acting β_2-agonist combination product, with mixed results. Dahl et al compared the two medication combinations and reported that budesonide-formoterol failed to demonstrate a statistically significant difference compared to fluticasone-salmeterol in parameters such as morning and evening peak expiratory flow values, asthma symptoms, rescue medication usage, or asthma control, as well as no difference in the severity of exacerbations or the mean rate of exacerbations over a 24 week period. Rosenhall et al looked at the efficacy of budesonide-formoterol in a single inhaler versus its individual components and found that there were no significant differences between the two groups in regards to lung function measurements, time to first exacerbation, or health-related quality of life.

The combination of an inhaled corticosteroid and long-acting β_2-agonist is currently the preferred controller combination regimen for patients $\geq$12 years of age with moderate-to-severe asthma for both the long-term control and prevention of symptoms. Budesonide and formoterol is a combination product that is FDA indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older. The individual components of this combination are also commercially available. Current national and international guidelines support the use of an inhaled corticosteroid with a long-acting β_2-agonist as treatment for patients with moderate-persistent to severe-persistent asthma that is inadequately controlled with inhaled corticosteroid monotherapy.

There are numerous studies that have evaluated the efficacy of the combination of budesonide, a corticosteroid, and formoterol, a long-acting β_2-agonist, in the treatment of asthma and have found that this combination resulted in improved lung function, including peak expiratory flow, forced expiratory volume in 1 second values, and a reduction in the use of daily rescue medications. Head-to-head studies have compared budesonide-formoterol to fluticasone-salmeterol with mixed results. Although the combination of budesonide and formoterol has shown to be efficacious compared to monotherapy, guidelines state that patients should be initiated on inhaled corticosteroid monotherapy if they are classified as having mild-to-moderate disease.

Therefore all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over the other alternatives in general use.

No brand budesonide and formoterol combination product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Altabax® (retapamulin) AHFS 840404 Skin and Mucous Membrane Antibacterials
Manufacturer comments on behalf of these products:
Altabax® (retapamulin)-GlaxoSmithKline

Dr. Gagnon noted that retapamulin is the first FDA-approved drug in a new class of antibacterials called the pleuromutilins. This antibacterial ointment was approved in April 2007 for the treatment of impetigo due to *S aureus* (methicillin-susceptible isolates only) or *S pyogenes*.

Guidelines for the treatment of impetigo were discussed. The Infectious Diseases Society of America (IDSA) skin and soft-tissue infection guidelines state that the decision to treat impetigo depends on the number of lesions, their location, and the necessity to prevent the spread of infection to others, and that the most effective topical agent for patients presenting with limited lesions is mupirocin. It is important to note that these guidelines were published prior to the FDA approval of retapamulin.

Dr. Gagnon noted that there are currently no documented drug interactions reported with retapamulin. The effect of concurrent application of retapamulin and other topical products to the same area of the skin has not been studied at this point in time. Application-site irritation and headache were reported as the most common drug-related adverse events associated with retapamulin.

Clinical studies evaluating the safety and efficacy of retapamulin were discussed. A trial by Oranje et al compared retapamulin to sodium fusidate ointment, an agent which is not available in the United States, in the treatment of impetigo. Overall clinical and bacteriological success rates were over 90% for both treatment groups in the clinical per-protocol populations with the success rates being significantly higher in the ratapamulin group. Two trials reported similar cure rates for retapamulin ointment and an oral antibiotic, cephalexin, when used to treat other skin infections.

Retapamulin, a topical antibacterial agent, is FDA approved for the treatment of impetigo due to *S aureus* (methicillin-susceptible only) or *S pyogenes*. Retapamulin's unique mechanism of action enables it to have a low propensity of bacterial resistance. In order to preserve this benefit, the manufacturer recommends that retapamulin should be prescribed only when there is strong proof or evidence regarding the presence of susceptible bacteria. Although there have been reports of bacterial resistance to mupirocin ointment, it is currently recognized as a first-line topical treatment option for impetigo by the IDSA.

There are limited published clinical trials evaluating the safety and effectiveness of retapamulin ointment. Currently there are no published studies comparing retapamulin to mupirocin, which is available in a generic ointment for the treatment of impetigo.

At this time, there is insufficient data to conclude that retapamulin is safer or more efficacious than other brands, generics and OTC products in this class and offers a significant clinical advantage over other alternatives in general use.

No brand retapamulin is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Mr. Main inquired if retapamulin had been studied in community acquired methicillin-resistant *Staphylococcus aureus*. Dr. Gagnon replied that no trials have evaluated this as a clinical outcome.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

7. RESULTS OF VOTE ANNOUNCED

Dr. Littlejohn announced the results of voting for each of the therapeutic classes. Results of voting are described in the Appendix to the minutes.

8. NEW BUSINESS

Dr. Littlejohn thanked MedMetrics for their hard work and preparation of high level reviews over the duration of the contract. There was no other new business.

9. NEXT MEETING DATE

The next P&T Committee Meeting is scheduled for 9:00 a.m. on August 13, 2008.

10. ADJOURN

The meeting was adjourned at 12:30 p.m.

Appendix

RESULTS OF THE BALLOTING
Alabama Medicaid Agency
Pharmacy and Therapeutics Committee
May 14, 2008

A. **Recommendation**: No brand platelet-aggregation inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action

B. **Recommendation**: No brand antiarrhythmic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action

C. **Recommendation**: No brand cardiotonic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

R Moore MD	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Medical Director								
Kathy Hall	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner								
	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner								

D. **Recommendation**: No brand miscellaneous cardiac drug is recommended for preferred status, regardless of cost.

Amendment: None

Vote: Unanimous to approve as recommended

R Moore MD	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Medical Director								
Kathy Hall	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner								
	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner								

E. **Recommendation**: No brand bile acid sequestrant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

R Moore MD	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Medical Director								
Kathy Hall	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner								
	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner								

F. **Recommendation**: No brand cholesterol absorption inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

G. **Recommendation**: No brand fibric acid derivative is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

H. **Recommendation**: No brand single entity HMG-CoA reductase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

I. **Recommendation**: No brand combination HMG-CoA reductase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

J. **Recommendation**: Prescription niacin is recommended for preferred status. Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand prescription niacin product is selected as a preferred agent.

No brand omega-3 acid ethyl ester is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

K. **Recommendation**: No brand nitrate or nitrite is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brand.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

L. **Recommendation**: No brand fluticasone furoate is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

M. **Recommendation**: No brand budesonide and formoterol combination product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

N. **Recommendation**: No brand retapamulin is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

Respectfully submitted,

5/14/08

James Gagnon, Pharm.D. Date